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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Substituted Pyridine N-Oxides, Processes for Their Preparation, and Their Use

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(30) (DE) P 41 42 989.3 1991/12/24

(57) 14 Claims

Abstract

Substituted pyridine N-oxides, processes for their preparation, and their use

Pyridine N-oxides which are substituted by ester and/or amide groups in the 2 and 4 or 5 positions, and a process for their preparation, are described. The compounds mentioned act as inhibitors of lysine hydroxylase and proline hydroxylase.

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Substituted pyridine N-oxides, processes for their preparation, and their use

Compounds which inhibit the enzymes proline hydroxylase and lysine hydroxylase have the effect of a very selective inhibition of collagen biosynthesis by influencing the collagen-specific hydroxylation reactions. In the course thereof, protein-bound proline or lysine is hydroxylated by the enzymes proline hydroxylase or, respectively, lysine hydroxylase. If this reaction is suppressed by inhibitors, a non-functional, hypohydroxylated collagen molecule is formed, which can be released by cells into the extracellular space in only a small amount. The hypohydroxylated collagen moreover cannot be incorporated into the collagen matrix, and is very readily broken down proteolytically. As a consequence of these effects, the total amount of collagen deposited in the extracellular space is reduced.

Inhibitors of proline hydroxylase are therefore suitable substances in the therapy of diseases in which the deposition of collagen contributes decisively to the syndrome. These include, inter alia, fibroses of the lung, liver and skin (scleroderma), as well as atherosclerosis.

It is known that inhibition of proline hydroxylase by known inhibitors, such as α,α'-dipyridyl, leads to an inhibition of the $C1_q$ biosynthesis of macrophages (W. Müller et al., FEBS Lett. 90 (1978), 218; Immunobiology 155 (1978), 47). This results in a failure of the classical route of complement activation. Inhibitors of prolin hydroxylas th r for also act as immunosuppr ssants, for xampl in cas s of immune complex diseases.

It is known t!.1t th nzym proline hydroxylas is inhibit d ff ctively by pyridin -2,4- and

-2,5-dicarboxylic acid (K. Majamaa et al., Eur. J. Biochem. 138 (1984) 239-245). However, these compounds are active as inhibitors in the cell culture only in very high concentrations (Tschank, G. et al., Biochem. J. 238 (1987) 625-633).

Pyridine-2,4- and -2,5-dicarboxylic acid diesters having 1-6 carbon atoms in the ester alkyl part are described in DE-A 34 32 094 as medicaments for inhibition of proline hydroxylase and lysine hydroxylase.

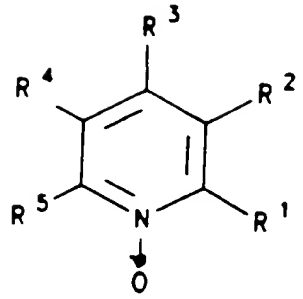
These lower-alkylated diesters have the disadvantage, however, that they are split into the acids too quickly in the organism, and do not arrive at their action site in the cell in a sufficiently high concentration, and are therefore not particularly suitable for possible administration as medicaments.

DE-A 37 03 959, DE-A 37 03 962 and DE-A 37 03 963 describe in general form mixed esters/amides, higher-alkylated diesters and diamides of pyridine-2,4- and -2,5-dicarboxylic acid which effectively inhibit collagen biosynthesis in an animal model.

2,4- and 2,5-disubstituted pyridine N-oxides are described in German Patent Application P 40 20 570.3.

It has now been found that substituted pyridine N-oxides of the following formula I and the physiologically tolerated salts also effectively inhibit lysine hydroxylase and proline hydroxylase.

The invention therefore relates to substituted pyridine N-oxid s of the general formula I



(I)

in which

R^1 and R^3 or R^4 are $-C(O)-X-R^6$, in which
X is O or $-N(R^7)-$ and
R^6 and R^7 are identical or different, and

A are a branched or unbranched, aliphatic or cycloaliphatic (C_1-C_{12})-alkyl radical or (C_1-C_{12})-alkenyl radical or a (C_1-C_{12})-alkynyl radical,

which is unsubstituted or mono- or polysubstituted, preferably mono- or disubstituted, by halogen, in particular fluorine, chlorine or bromine, hydroxyl, cyano, carboxyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino,

(C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, are substituted by 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, hydroxy, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_nC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, trifluoromethyl, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl and N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR', or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical or heteroaryl radical which carries 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, nitro, cyano, carboxyl, hydroxyl, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2]_nC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl,

(C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, can be substituted by 1,2,3,4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl and (C_1-C_6)-alkoxy, or by

an unsubstituted or substituted (C_6-C_{12})-aryloxy radical, (C_7-C_{11})-aralkyloxy radical or heteroaryloxy radical, which carries 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_zH_{(2z+1-s)}F_s$, $-OCF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl,

N,N-di-(C_1-C_6)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl and N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl, is optionally substituted by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR', or by

a radical of the general formula II

$$-O-R^8 \qquad (II)$$

in which

R^8 is an amino acid bonded via its acyl radical, a derivative of this amino acid or an alcohol-protective group,

B are an unsubstituted or substituted (C_6-C_{12})-aryl radical or (C_7-C_{11})-aralkyl radical or a heteroaryl radical, which is mono- or polysubstituted, preferably mono- or disubstituted, by

hydroxyl, halogen, cyano, carboxyl, amino, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkylcarbonyloxy, (C_1-C_8)-alkylamino, di-(C_1-C_6)-alkylamino, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_nC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl or N,N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy,

cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido,

C in the case where X = -N(R^7), are an unsubstituted or substituted (C_1-C_{12})-alkoxy radical, (C_3-C_8)-cycloalkoxy radical or (C_6-C_{12})-aryloxy radical or a (C_7-C_{11})-aralkyloxy radical, which is mono- or polysubstituted, preferably mono- or disubstituted, by

halogen, trifluoromethyl, (C_1-C_6)-alkoxy, hydroxyl, (C_1-C_6)-hydroxyalkyl, NR'R" or cyano,

in which, in each case,

R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_7-C_{11})-aralkylcarbonyl or (C_6-C_{12})-arylcarbonyl

or form a saturated h t rocyclic ring, preferably a 5- or 6-membered ring, with th nitrogen,

and

R^2, R^3 and R^4 or R^3, if R^4 or R^3 has not already been defined above, are identical or different and

D are hydrogen, at least one radical R^2, R^3 and R^4 or R^3 being other than hydrogen, halogen, in particular fluorine, chlorine or bromine, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_3-C_8)-cycloalkyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, (C_1-C_{12})-alkoxycarbanoyl, (C_1-C_{12})-alkylcarbanoyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino-(C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, $NR'R''$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkylsulfonamido or arylsulfonamido, in which the aryl and aralkyl radicals present in the above

substitu nts can also be het rocyclic in nature and/or are substituted, as is also th ca for alkyl, with 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, trifluoromethyl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl and N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or

E are an alkyl, alkenyl or alkynyl radical having up to 9 carbon atoms, which is optionally substituted by

1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for xampl , pyrrolidino, piperidino or their het rocyclic d rivativ s morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino,

N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{11})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cyclo-alkanoylamino, (C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',
or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',
or

F denote a substituted or unsubstituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore

carries in the aryl part 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino, morpholino, thiomorpholino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular up to 3 of the abovementioned identical or different substituents, and in which a CH_2 group of the aryl chain is optionally replaced by O, S, SO, SO_2 or NR', or

G are a substituent of the formulae $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen, alkyl, alkenyl or alkynyl, in each case having up to 9 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which

carries in the aryl part 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, carboxyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmer-

capto, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_6)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_6)-alkanediylamino, such as, for example, pyrrolidino, piperidino, morpholino, thiomorpholino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular up to 3 of the abovementioned identical or different substituents, and in which a CH_2 group of the aryl chain is optionally replaced by O, S, SO, SO_2 or NR',

and

n = 0 or 1,

f = 1 to 8, preferably 1 to 5,

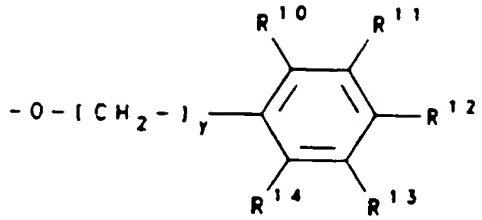
g = 0.1 to (2f + 1) and

x is 0, 1, 2 or 3, preferably 0 or 1,

plus all derivatives which carry a corresponding protective group in their amino or hydroxyl groups, and the physiologically active salts.

Aryl, aryloxy, heteroaryl and heteroaryloxy compounds are understood as meaning, in particular, phenyl and naphthyl rings and unsubstituted 5- and 6-membered heteroaromatic rings having 1 ,2 or 3 nitrogen and/or oxygen and/or sulfur atoms, such as pyridyl, pyridazyl, pyrimidyl, pyrazyl, imidazolyl, triazolyl, thienyl, oxazolyl and thiazolyl d rivatives, and benzo-fused derivatives thereof. Th radical (C_7-C_{11})-aralkyloxy is preferably understood as meaning a substituted phenylalkyloxy

radical of the formula III



(III)

in which R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'R", such as amino, anilino or N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or two adjacent substituents together are a $-[CH_2-]_n$ or $-CH=CH-CH=CH-$ chain, in which a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR', Y is 1, 2, 3 or 4, preferably 0 or 1, and the other substituents R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are as defined above.

Of the amino acids mentioned, the naturally occurring α-amino acids are particularly preferred.

Amino-protective groups are understood as meaning, in particular, those groups which are described in R. Geiger and W. König "The Peptides" Volume 3, "Protection of Functional Groups in Peptide Synthesis", E.G. Gross, J. Meienhofer Edit, Academic Press, New York (1981), in particular pages 7 - 46.

Such groups are likewise described in A. Hubbuch, Schutzgruppen in der Peptidsynthese [Protective Groups in Peptide Synthesis], Kontakte 3/79, pages 14-23.

The following amino-protective groups are particularly preferred:

acetamidomethyl,
1-adamantyloxycarbonyl,
1-(1-adamantyl)-1-methyl-ethoxycarbonyl,
allyloxycarbonyl,
tert-butyloxycarbonyl,
1-(4-biphenylyl)-1-methyl-ethoxycarbonyl,
dicyclohexylcarbodiimide,
α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl,
4-dihydroxyborylbenzyloxycarbonyl,
9-fluorenylmethyloxycarbonyl,
1-hydroxybenzotriazole,
3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine,
isobornyloxycarbonyl,
1-methyl-cyclobutyloxycarbonyl,
4-methoxybenzyloxycarbonyl,
methylsulfonylethyloxycarbonyl,
4-pyridylmethyloxycarbonyl,
2,2,2-trichloro-tert-butyloxycarbonyl,
benzyloxycarbonyl,
halogen-substituted benzyloxycarbonyl,
4-nitro-benzyloxycarbonyl,
2-phosphonoethyloxycarbonyl,
phenylsulfonylethoxycarbonyl,
toluenesulfonylethoxycarbonyl,
2,3,5-trimethyl-4-methoxy-phenylsulfonyl and
benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphat .

Preferred compounds of the formula I in which the amino groups are protected are those in which the protected amino groups are part of this amino acid R^9.

Possible alcohol-protectiv groups are, in particular, substituted or unsubstitut d methyl ethers, thyl ethers, benzyl ethers, silyl ethers, esters, carbonates or sulfonates.

These include the following compounds:

As substituted methyl ethers:
methoxymethyl, methylthiomethyl, t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxybenzyloxymethyl, (4-methoxyphenoxy)-methyl, guaiacolmethyl, t-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis-(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl-S,S-dioxo, 1-[2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl and tetrahydrothiofuranyl.

As substituted ethyl ethers:
1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl and benzyl.

As substituted benzyl ethers:
p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halogenobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl-N-oxido, diphenylmethyl, p,p'-dinitrobenzohydryl, triph nylm thyl, α-naphthyldiphenylm thyl, p-methoxyphenyldiphenylmethyl, di(-p-methoxyphenyl)phenylmethyl, tri(p-methoxyph nyl)methyl, 4-(4'-bromoph nacyloxy)ph nyldiphenylm thyl, 4,4',4''tris(4,5-dichloro-

phthalimidophenyl)methyl, 4,4',4"-tris(levulinooxyph n-yl)methyl, 4,4',4"-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1,4'-methyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-bis-(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl.

As silyl ethers:
trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl and t-butylmethoxyphenylsilyl.

As esters:
formates, benzoylformates, acetates, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, p-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate and 2,4,6-trimethylbenzoate (mesitoate).

As carbonates:
methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, p-nitrophenyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, S-benzyl thiocarbonates, 4-ethoxy-1-naphthyl and methyl dithiocarbonates.

Further esters:
2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyac tat , 2,4-bis-(1,1-dim thylpropyl)phenoxyac tate, chlorodiphenylac tate, isobutyrate, monosuccinate, (E)-2-methyl-2-butenoate (tigloate), o-(methoxycarbonyl)benzoate, p-P-benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-t tramethylphos-

phorodiamidat , N-phenylcarbamat , borates, dimethylphosphinothioyl and 2,4-dinitrophenylsulfenate.

As sulfonates:
sulfates, methanesulfonate (mesylate), benzylsulfonate and tosylates.

The following protective groups are particularly preferred:
(C_1-C_6)-alkanoyl, (C_1-C_8)-alkylcarbamoyl, di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, (C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{11})-aralkyloxycarbonyl, in particular benzyloxycarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{11})-aralkylcarbonyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, carbamoyl-(C_1-C_6)-alkyl esters, (C_1-C_{10})-acyloxy-(C_1-C_6)-alkyl, preferably (C_1-C_{10})-alkanoyloxy-(C_1-C_6)-alkyl, benzyloxy-(C_1-C_6)-alkyl, benzyloxycarbonyloxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxycarbonyloxy-(C_1-C_6)-alkyl, amino acid esters and tetrahydropyranyl.

Preferred compounds of the formula I are those in which R^1 and R^3 or R^4 are $-C(O)-X-R^6$, in which
X is $-N(R^7)-$.

Compounds of the formula I which are furthermore preferred are those in which
R^6 is hydrogen or methyl and
R^7 has the abovementioned meaning,
R^6 and R^7 are hydrogen and/or methyl, if at least one group R^1, R^3 or R^4 is a radical $-C(O)-N(R^7)-R^6$, in which R^6 and/or R^7 have the abovementioned meaning.

If R^6 or R^7 is not hydrogen or m thyl according to the above pref rred embodim nt, th following compounds ar pref rred, in which the radicals

A are a branched or unbranched (C_1-C_{12})-alkyl radical, which is unsubstituted or mono- or polysubstituted by

halogen, in particular fluorine, chlorine, bromine, hydroxyl, cyano, carboxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxy-carboxyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_7-C_{11})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbamoyloxy or N-(C_6-C_{12})-arylcarbamoyloxy, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature, and/or, as is also the case for alkyl, are substituted by 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, hydroxyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_3)-alkoxycarbonyl, carbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from the series comprising halogen, nitro, cyano, carboxyl, hydroxyl, trifluoromethyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, NR'R", N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_1-C_3)-alkylcarbonyloxy, aminoalkyl and N-(C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, in which R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl or (C_1-C_4)-alkyl, or by

an unsubstituted or substituted (C_6-C_{10})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical, which carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl,

(C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxy, (C_1-C_3)-alkylmercapto, (C_1-C_3)-alkylsulfinyl, (C_1-C_3)-alkylsulfonyl, (C_1-C_3)-alkylcarbonyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy and NR'R", in which R' and R" are identical or different and are hydrogen, (C_6-C_{10})-aryl or (C_1-C_4)-alkyl, or by

a radical of the formula II

$$-O-R^8 \qquad (II)$$

in which

R^8 is an amino acid bonded via its acyl radical, or is a derivative thereof,

B denote a (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl or phenethyl, which are unsubstituted or monosubstituted by halogen, cyano, carboxyl, hydroxyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkylcarbonyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-hydroxyalkyl, amino, (C_1-C_5)-alkylamino, di-(C_1-C_5)-alkylamino, (C_1-C_5)-alkanoylamino, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyloxy or N,N-di-(C_1-C_4)-alkylcarbamoyloxy or

C are an unsubstituted (C_1-C_8)-alkoxy radical, (C_3-C_8)-cycloalkoxy radical, (C_6-C_{12})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical.

Particularly preferred compounds of the formula I are those in which R^6 and R^7, if these are not hydrogen or methyl, as described above, are

A an unbranched (C_1-C_{12})-alkyl radical, which is unsubstituted or monosubstitut d by

hydroxyl, halogen, (C_1-C_8)-alkoxy, (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy-carbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyl-oxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbonyloxy, N-(C_6-C_{12})-arylcarbanoyloxy, (C_1-C_5)-alkanoylamino, (C_3-C_6)-cycloalkanoylamino, (C_6-C_{12})-aroylamino or (C_7-C_{11})-aralkanoylamino, in which alkyl, aryl, aryloxy, aralkyl or aralkyloxy in turn are substituted by hydroxyl, halogen, in particular fluorine, (C_1-C_3)-alkyl or (C_1-C_3)-alkoxy, or by

a phenyl radical which is unsubstituted or monosubstituted by a hydroxyl group, a phenoxy or benzyloxy radical which is unsubstituted or substituted by hydroxyl, halogen or (C_1-C_4)-alkoxy, or by

a radical of the formula II

$$-O-R^8 \qquad (II)$$

in which R^8 is an amino acid bonded via its acyl radical, or its derivative substituted on the amino group, or

B are a (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl or phenethyl, which is unsubstituted or monosubstituted by hydroxyl.

In respect of the substituents R^2, R^5 and R^4 or R^3, if R^3 or R^4 is not already defined as above, compounds in which not more than two of the three radicals are preferably other than hydrogen, particularly preferably not more than one of the radicals is other than hydrogen, are preferred.

Compounds which are furth rmor pref rred are thos in which, independently of one another, R^2, R^5 and R^4 or R^3 are other than hydrogen if these are directly adjacent to not more than one other substituent R^1 and R^3 or R^4.

R^2, R^5 and R^4 or R^3, if R^4 and R^3 are not already defined above and are not to be hydrogen, are preferably

D halogen, in particular fluorine, chlorine or bromine, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_3-C_8)-cycloalkyl, (C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, (C_1-C_6)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_6)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, NR'R", (C_1-C_8)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl or (C_3-C_8)-cycloalkylcarbonyl, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, are substitut d by 1, 2 or 3 identical or different substituents from th series comprising halog n, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'R",

phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl,

or

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substituted by 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_zH_{(2z+1-g)}F_g$, $-OCF_2-CHFCl$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_6)-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_6)-alkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_6)-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino,
or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy, $[CH_2-]_xC_zH_{(2z+1-g)}F_g$, ($C_1$-$C_6$)-alkylcarbonyl, ($C_1$-$C_6$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_6)-alkylamino, N-(C_7-C_{11})-

aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_6)-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_6)-hydroxyalkanoylamino, (C_1-C_5)-alkoxy-(C_1-C_6)-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino,

or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, ($C_1$-$C_6$)-alkylcarbonyl, ($C_1$-$C_6$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino,

or

G a substituent of the formula $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen, alkyl or alkenyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which carries 1, 2 or 3 identical or different substituents from the s ries comprising halogen, hydroxyl, cyano, nitro, carboxyl, trifluorom thyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, ($C_1$-$C_6$)-alkylcarbonyl, ($C_1$-$C_6$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-

cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino.

Of these, compounds of the formula I which are preferred are those in which

R^2, R^5 and R^4 or R^3, if R^4 and R^3 are not already defined above and are not to be hydrogen, are

D halogen, in particular fluorine, chlorine or bromine, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino or N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, can be substituted by 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$ and NR'-R, or

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substituted by 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino and di-N,N-(C_1-C_6)-alkylamino, or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from

th s ries comprising hydroxyl, halogen, trifluorom thyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, amino, N-(C_1-C_{10})-alkylamino and di-N,N-(C_1-C_{10})-alkylamino, or

G a substituent of the formula $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen or alkyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which contains 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, amino, N-$(C_1-C_{10})$-alkylamino and di-N,N-$(C_1-C_{10})$-alkylamino.

Particularly preferred compounds of the formula I ar those in which

R^2, R^5 and R^4 or R^3, if R^4 and R^3 are not alr ady d fin d abov and ar not to be hydrog n, ar

D halog n, in particular fluorin , chlorin or bromine, trifluorom thyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$,

$-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino or N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, or:

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substituted by 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino and di-N,N-(C_1-C_6)-alkylamino, or by an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl and (C_1-C_6)-alkoxycarbonyl, or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical or (C_7-C_{11})-aralkyl radical, in which the aryl radical mentioned is, in particular, phenyl or naphthyl and which furthermore carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkylcarbonyl and (C_1-C_6)-alkoxycarbonyl, or

G a substituent of the formula $-OR^8$ or $-N(R^8)_2$, in which

R^8 is hydrogen or alkyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which contains 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, amino, N-(C_1-C_{10})-alkylamino and di-N,N-(C_1-C_{10})-alkylamino.

Th invention furthermor relates to the use of compounds of the formula I and physiologically tolerated salts thereof for the preparation of a proline hydroxylase-inhibiting and lysine hydroxylase-inhibiting medicament.

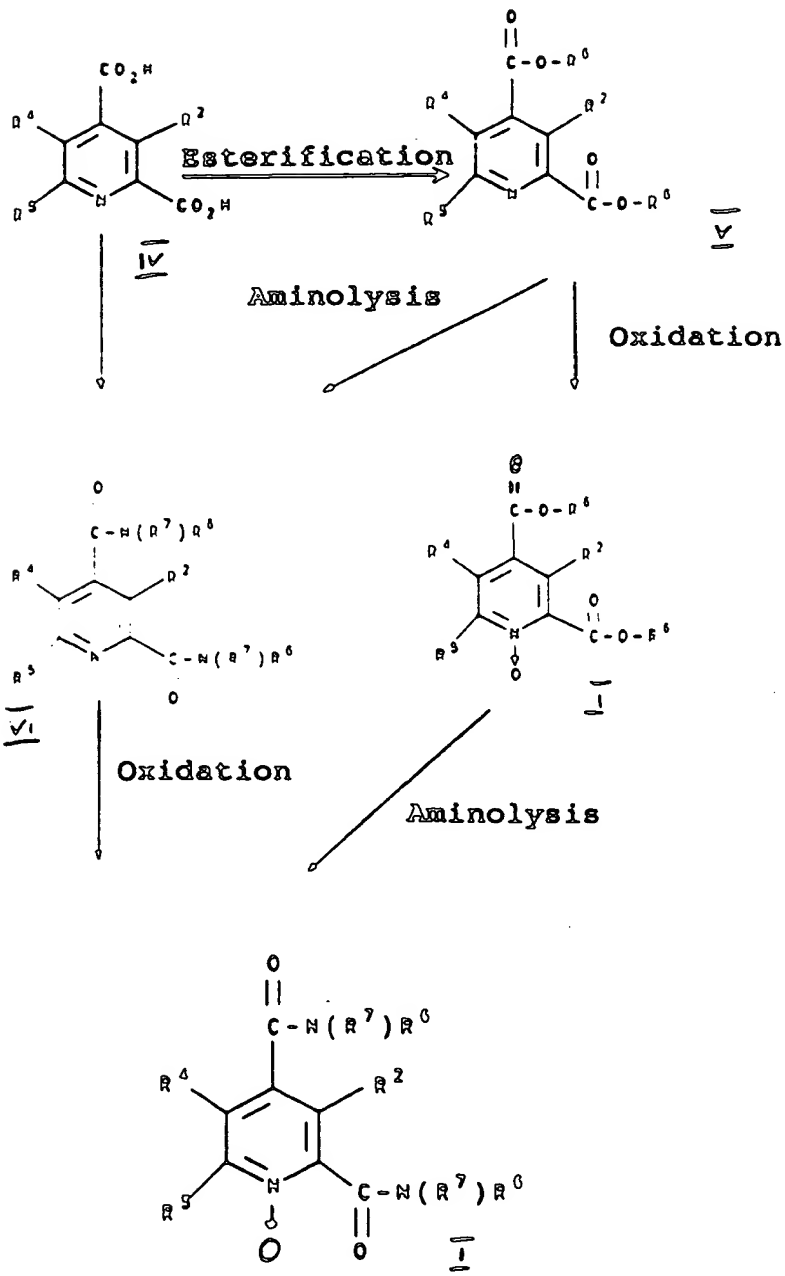
Finally, the invention relates to the compounds of the formula I for use as medicaments.

In particular, the invention relates to the compounds of the formula I for use as fibrosuppressants and immunosuppressants and for inhibition of proline hydroxylase and lysine hydroxylase, and for influencing the metabolism of collagen and collagen-like substances and the biosynthesis of C1q.

The invention furthermore relates to a process for the preparation of compounds of the formula I.

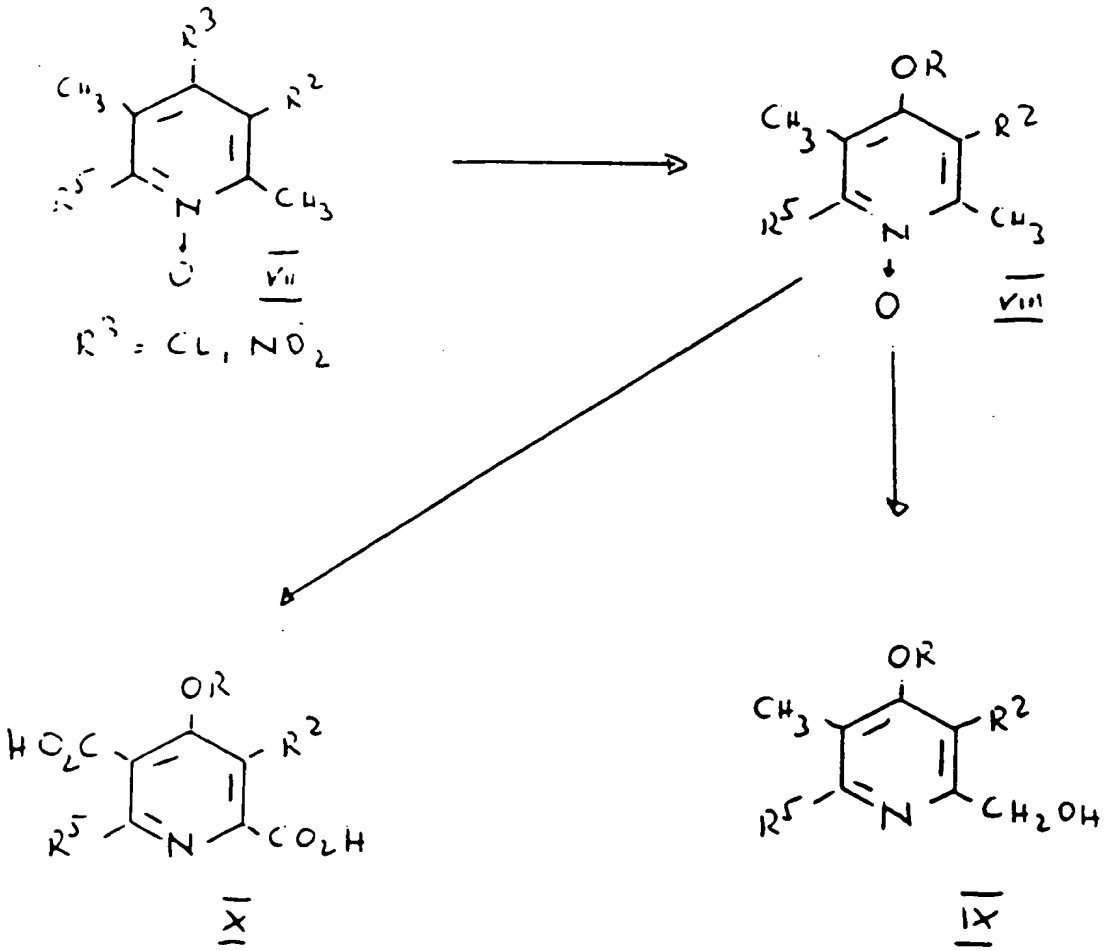
The following Equation I applies to the preparation of 2,4-disubstituted pyridine N-oxide derivatives. However, in principle, it can also be used to illustrate the preparation of 2,5-disubstituted pyridine N-oxide derivatives, and for mixed derivatives (esters/amides).

Equation I


Esterification
Aminolysis
Oxidation
Oxidation
Aminolysis

Substitut d pyridine-2,4- and -2,5-dicarboxylic acids of the formula IV are obtain d, for xample, by oxidation from the corresponding dimethylpyridines VII or VIII or the corresponding methyl-2-hydroxymethylpyridines IX. The preparation of the dimethylpyridines VII and VIII in turn is described in R.J. Ife, J. Med. Chem. 32, 1970-1977 (1989) and the literature cited therein. The following Equation II gives an indication of this. On the basis of this equation, the substituted pyridine derivatives according to the invention are accessible to the expert. A particular example is 2,5-dimethyl-3,4-dichloropyridine.

Equation II



Compounds of the formula VII are converted into compounds of the formula VIII with alcohols ROH and a base in dimethylformamide or dimethylacetamide at 20 to 150°C. Compounds of the type IX are prepared by reactions of VIII with acetic anhydride/acetic acid at 120°C and subsequent reaction with NaOH/methanol at 25°C. The oxidation to give compound X with sodium permanganate in water at 70 to 100°C can be carried out starting from VIII or IX. The dicarboxylic acids X can be either esterified and oxidized to give the N-oxides I according to the invention in accordance with Equation I, or - also in accordance with Equation I - converted into amides and oxidized.

The preparation of the compounds of type IV is described in the following literature references. This preparation is the introduction of the substituents R^2, R^4 and R^5 into the 2,4- or 2,5-pyridine-dicarboxylic acid.

Starting with the compound of the formula IV, the amide VI can be prepared either directly from IV or via the ester V.

The reaction of V or VI to give the amides I or esters I is carried out under conditions analogous to those in P 40 20 570.3.

For this, an oxidizing agent, such as, for example, hydrogen peroxide or peracids, such as peracetic acid, perfluoroacetic acid, perbenzoic acid or metachloroperbenzoic acid, in solvents, such as chlorinated hydrocarbons, such as, for example, methylene chloride, chloroform, tri- or tetrachloroethylene, benzene or toluene, is added to the pyridine compounds to be oxidized, which can likewise be dissolved in the abovementioned solvents, and the mixture is stirred at a temperature of between -30 and +40°C, preferably 0 and 25°C, for between 30 minutes and 3 days. The end of the reaction can be determined,

for example, by means of thin layer chromatography. Preferably, the compounds according to the invention can be prepared by employing the pyridine derivative and the oxidizing agent in equimolar amounts or with up to an approximately 5-fold excess of oxidizing agent.

If appropriate, an excess of peracid can also be eliminated, for example, by passing gaseous ammonia into the reaction solution and separating off the resulting precipitate from the reaction solution by filtration.

If appropriate, the product can be worked up, for example, by extraction or by chromatography, for example over silica gel. The product isolated can be recrystallized.

General instructions for this oxidation method are also described, for example, in "E. Lingsberg, Pyridine and its Derivatives, Interscience Publishers, New York, 1961, Part 2, 93".

The oxidation with hydrogen peroxide is described, for example, in "E. Ochiai, J. Org. Chem. 18, 534 (1953)".

The conditions for an aminolysis of the ester I to give the amide I correspond to those used for the reaction of V to give VI.

The preparation and the aminolysis are otherwise reaction types which are known as such. However, compounds of the formula I prepared by the above reactions are novel.

The process conditions can be seen in detail in German Patent Applications P 38 26 471.4, 38 28 140.6, 39 24 093.2 and 40 01 002.3, and DE-A-37 03 959, 37 03 962 and 37 03 963.

The compounds of the formula I according to the invention have useful pharmacological properties and exhibit, in particular, activity as inhibitors of proline hydroxylase and lysine hydroxylase, and as a fibrosuppressant, immunosuppressant and antiatherosclerotic.

The antifibrotic action can be determined using the model of liver fibrosis induced by carbon tetrachloride. For this, rats are treated twice weekly with CCl_4 (1 ml/kg) - dissolved in olive oil. The test substance is administered daily, if appropriate even twice daily, perorally or intraperitoneally - dissolved in a suitable tolerated solvent. The extent of the liver fibrosis is determined histologically, and the amount of collagen in the liver is analysed by hydroxyproline determination - as described by Kivirikko et al. (Anal. Biochem. 19, 249 et seq. (1967)). The fibrogenesis activity can be determined by radioimmunological assay of collagen fragments and procollagen peptides in the serum. The compounds according to the invention are active in a concentration of 1 - 100 mg/kg in this model.

The fibrogenesis activity can be determined by radioimmunological assay of the N-terminal propeptide of collagen type III or of the N- and C-terminal crosslinking domains of collagen type IV (7s-collagen or type IV collagen-NC_1) in the serum.

For this purpose, the hydroxyproline, procollagen III peptide, 7s-collagen and type IV collagen-NC concentrations were measured in the liver of

a) untreated rats (control)

b) rats to which carbon tetrachloride had been administered (CCl_4 control)

c) rats to which first CCl_4 and then a compound according to th invention had been administered

(this t st method is described by Rouill r, C., experimental toxic injury of the liver; in The Liver,

C. Rouiller, Vol. 2, 5. 335-476, New York, Academic Press, 1964).

Another model for evaluation of the antibiotic action is that of bleomycin-induced pulmonary fibrosis as described by Kelley et al. (j. Lab. Clin. Med. 96, 954, (1980)). The model of the cotton-wool swab granuloma as described by Meier et al., Experimentia 6, 469 (1950) can be used to evaluate the action of the compounds according to the invention on granulation tissue.

The compounds of the formula I can be used as medicaments in the form of pharmaceutical preparations which comprise them, if appropriate together with tolerated pharmaceutical excipients. The compounds can be used as medicines, for example in the form of pharmaceutical preparations which comprise these compounds as a mixture with a pharmaceutical, organic or inorganic excipient which is suitable for enteral, percutaneous or parenteral administration, such as, for example, water, gum Arabic, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly and the like.

For this purpose, they can be administered orally in doses of 0.1 - 25 mg/kg/day, preferably 1 - 5 mg/kg/day, or parenterally in doses of 0.01 - 5 mg/kg/day, preferably 0.01 - 2.5 mg/kg/day, in particular 0.5 - 1.0 mg/kg/day. In serious cases, the dosage can also be increased. However, lower doses are also sufficient in many cases. These data relate to an adult weighing about 75 kg.

The invention furthermore r lates to the use of the compounds according to the inv ntion in the pr paration of m dicaments employed for the treatment and prophylaxis of the abovementioned metabolic disturbances.

The invention furthermore relates to medicaments which comprise one or more compounds of the formula I according to the invention and/or physiologically tolerated salts thereof.

The medicaments are prepared by processes which are known per se and familiar to the expert. As medicaments, the pharmacologically active compounds according to the invention (= active compound) are employed either as such or, preferably, in combination with suitable pharmaceutical auxiliaries or excipients, in the form of tablets, coated tablets, capsules, suppositories, emulsions, suspensions or solutions, the active compound content being up to about 95 %, advantageously between 10 and 75 %.

Suitable auxiliaries or excipients for the desired medicament formulation are, for example, in addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, also antioxidants, dispersing agents, emulsifiers, foam suppressants, flavor correctants, preservatives, solubilizing agents or dyestuffs.

The following examples are intended to illustrate the invention.

Example 1

5-Bromo-pyridine-1-oxide-2,4-dicarboxylic acid bis-[(3-methoxypropyl)amide]

a) 5-Bromo-2,4-dimethylpyridine

150 ml of 65 % strength oleum are added dropwise to 28.9 ml of 2,4-dim thylpyridine, while cooling with ice and stirring, such that the temperature does not rise above 35°C. When the solution has become homog nized,

6.42 ml of bromine are slowly added dropwise. The mixture is stirr d at 80°C for 3½ hours. After cooling, it is allowed to drip carefully onto 1 kg of ice, and the resulting mixture is neutralized with solid Na_2CO_3 and extracted 3 times with 300 ml of ether each time. The organic layer is separated off and dried over magnesium sulfate. After removal of the solvent by distillation in vacuo, 34.6 g of a pale yellow oil which comprises the isomers 5-bromo-2,4-dimethylpyridine and 3-bromo-2,4-dimethylpyridine are obtained. The isomers are separated by column chromatography on silicon dioxide gel to give 10 g of 5-bromo-2,4-dimethylpyridine as a colorless liquid (13.0 g of 3-bromo-2,4-dimethylpyridine).
Yield: 22 %.

b) 5-Bromo-pyridine-2,4-dicarboxylic acid

4 g of 5-bromo-2,4-dimethylpyridine from Example 1 are heated to 70-80°C in 200 ml of water and 2.4 g of KOH. Half of 12.74 g of potassium permanganate is then introduced in portions. The solution is heated to the boiling point and the remainder of the potassium permanganate is added. The mixture is stirred at 70-80°C for 20 hours and then filtered hot with suction, and the precipitate is washed 4 times with 50 ml portions of hot water. The combined filtrates are concentrated to 100 ml in vacuo. The solution is brought to pH 1 with concentrated hydrochloric acid and is left to stand at 0°C for 20 hours. The crystalline solid is filtered off with suction and dried in vacuo at 100°C. The yield is 2.9 g.
Melting point 261-263°C.

c) 5-Bromo-pyridine-2,4-dicarboxylic acid bis-[(3-methoxypropyl)amid]

2.46 g (10 mmol) of 5-bromo-pyridine-2,4-dicarboxylic acid are suspend d in 70 ml of toluene and 0.2 ml of dimethylformamid , and 1.45 ml (20 mmol) of thionyl

chlorid are add d. The reaction mixture is heated at 110°C for 5 hours, during which a clear solution forms.

Th solution is then allowed to cool to 0°C, and a solution of 2.05 ml (20 mmol) of 3-methoxypropylamin and 2.8 ml of triethylamine in 10 ml of toluene is added dropwise.

The mixture is left to stand at 20°C for 12 hours and concentrated in vacuo, water is added, the mixture is extracted with methylene chloride, and the organic phase is dried and freed from the solvent to give the substance as a colorless oil, yield 2.2 g.

Empirical formula: $C_{15}H_{22}BrN_3O_4$ (388.26)
MS: m/e = 389 ($M + H^+$)

d) The above compound is dissolved in 80 ml of methylene chloride, and 5 mg of meta-chloro-perbenzoic acid are added in portions at 10°C. After 2 hours, a further 5 g of peracid are added, the mixture is heated at 42°C for 3 hours, a further 5 g of peracid are added, and the mixture is heated at 42°C for 5 hours.

Excess peracid and 3-chlorobenzoic acid are precipitated by passing in ammonia gas and are filtered off with suction. The solution is concentrated and the residue is chromatographed over silica gel using ethyl acetate/methanol 10:1. The title compound is obtained as colorless crystals. Melting point 94°C.

Empirical formula: $C_{15}H_{22}BrN_3O_4$ (404.26)
MS: m/e = 405 ($M + H^+$)

Example 2

Pyridine-1-oxid -2,4-dicarboxylic acid dimethyl ester

7.0 g (35.8 mmol) of pyridine-2,4-dicarboxylic acid dimethyl ester are dissolved in 200 ml of methylene chloride, and 6.2 g (36 mmol) of 3-chloroperbenzoic acid are added at 10°C. After 2 hours, a further 6.2 g of peracid are added, the mixture is allowed to stand overnight, a further 3.1 g of peracid are added, and the mixture is heated at 40°C for 5 hours (thin layer chromatography control).
Excess peracid and 3-chlorobenzoic acid are precipitated by passing in ammonia gas 3 times, and are filtered off. The solution is concentrated and the residue is crystallized from toluene, 4.5 g.

Melting point 132°C; R_f (SiO_2, ethyl acetate) = 0.29

Example 3

Pyridine-1-oxide-2-carboxylic acid methyl ester-4-carboxylic acid (2-benzyloxyethyl)amide and pyridine-1-oxide-2-carboxylic acid (2-benzyloxyalkyl)amide-4-carboxylic acid methyl ester

3.1 g (15 mmol) of the title compound from Example 2 are heated at 100°C in 50 ml of N,N-dimethylacetamide with 22.8 g (150 mmol) of 2-benzyloxyethylamine (prepared from 2-aminoethanol, sodium and benzyl chloride) for 1 hour. The mixture is allowed to cool and is concentrated, water is added, the mixture is extracted with methylene chloride and concentrated and the oily residue (4.8 g) is crystallized with ethyl acetate.

Melting point 76-78°C (colorless crystals)
Empirical formula: $C_{17}H_{18}N_2O_5$ (330)
MS: m/e = 331 ($M + H^+$)
The corresponding diamide was to be obtained after 10 hours at 140°C.

Example 4

4-Methoxy-pyridine-1-oxide-2,5-dicarboxylic acid bis-[(2-hydroxyethyl)amide]

a) 2-Hydroxymethyl-4-methoxy-5-methyl-pyridine

5.4 g (35 mmol) of 4-methoxy-2,5-dimethyl-pyridine N-oxide (melting point 102-104°C, diisopropyl ether; prepared from 2,5-dimethyl-pyridine N-oxide and sodium methylate in methanol) are dissolved in 30 ml of glacial acetic acid, and 40 ml of acetic anhydride are added dropwise at 80°C.

The mixture is heated at 115°C for 90 minutes and cooled to 80°C, 75 ml of methanol are added dropwise, the mixture is concentrated, the residue is taken up in methanol, 200 ml of 1.5 N methanolic sodium hydroxide solution are added dropwise, water is added, the mixture is extracted with methylene chloride, dried and concentrated and the residue is crystallized with cyclohexane, yield: 4.4 g; melting point 92-94°C.

b) 4-Methoxy-pyridine-2,5-dicarboxylic acid

2.3 g (15 mmol) of the compound from 4a) are suspended in a solution of 1 g of KOH in 75 ml of water, and 7.2 g (45 mmol) of $KMnO_4$ are added in portions at 70°C. The mixture is left at 80°C for a further hour, the magnesium dioxide which has been filtered off with suction is washed with water, and the filtrate is concentrated and brought to pH 1 with hydrochloric acid;
Yield: 1.45 g; melting point 231°C (decomposition).

c) 4-Methoxy-pyridin -1-oxide-2,5-dicarboxylic acid dimethyl est r

1.4 g of th compound from 4b) are h at d at th boiling point in 150 ml of methanol and 2 g of sulfuric acid (98 % strength) for 15 hours. The mixture is allowed to cool, saturated ammonium chloride solution is added, while cooling, and the mixture is extracted with methylene chloride and concentrated to give, analogously to Example 2 by reaction of the crude product with 3-chloroperbenzoic acid, 0.8 g of 4-methoxy-pyridine-2,5-dicarboxylic acid dimethyl ester N-oxide, melting point 134-136°C.

d) The title compound is obtained from the above compound of Example 4c) by reaction with excess 2-aminoethanol, colorless crystals, melting point 124-127°C (from ethyl acetate).

The following compounds were to be obtained analogously from the compound of Example 4c) by reaction with the corresponding amines:

4-methoxy-pyridine-2,5-dicarboxylic acid bis-[(2-methoxyethyl)amide] N-oxide
4-methoxy-pyridine-2,5-dicarboxylic acid bis-[(3-hydroxypropyl)amide] N-oxide
4-methoxy-pyridine-2,5-dicarboxylic acid bis-[(3-methoxypropyl)amide] N-oxide
4-methoxy-pyridine-2,5-dicarboxylic acid bis-[(2-benzyloxyethyl)amide] N-oxide

Example 5

Pyridine-1-oxide-2,4-dicarboxylic acid bis-N,N'-[2-(4-methylbenzoyloxy)ethyl]amide

a) Pyridine-2,4-dicarboxylic acid bis-N,N'-[2-(4-methylbenzoyloxy)ethyl]amide

b) 0.2 g of 4-N,N-dimethylaminopyridine and 0.8 ml (6 mmol) of triethylamine are added to 0.7 g (2.5 mmol) of pyridine-2,4-dicarboxylic acid bis-N,N'-(3-hydroxyethyl)amide in 100 ml of methylene chloride, and 0.6 ml (5 mmol) of 4-methylbenzoyl chloride are then added dropwise. After 1 hour, the mixture is concentrated and the residue is then taken up in water. After 1 hour, the mixture is extracted by shaking twice with water and the organic phase is concentrated. The crude product is chromatographed over silica gel using ethyl acetate.

Colorless crystalline powder: melting point 165-166°C
Empirical formula: $C_{27}H_{27}N_3O_6$ (489)
MS: m/e = 490 ($M + H^+$).

b) 0.31 ml of 30 percent strength H_2O_2 is added dropwise to a solution of 0.25 g of the above compound in 5 ml of 96 percent strength formic acid, and the mixture is heated at 80°C for 4 hours. It is then evaporated in vacuo and the crystalline residue is stirred with hot methanol and filtered off with suction. 0.18 g of pyridine-2,4-dicarboxylic acid N,N'-bis-[2-(4-methylbenzoyloxy)ethyl]amide is obtained as a colorless crystalline powder, melting point 186-188°C.
MS: m/e = 506 ($M^+ + H^+$).

Example 6

Pyridine-1-oxide-2,4-dicarboxylic acid N,N'-bis-[(2-benzoyloxyethyl)amide]

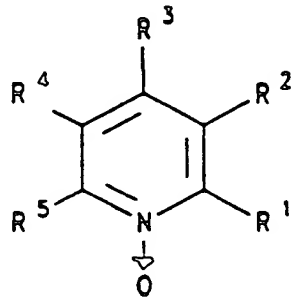
a) Pyridine-2,4-dicarboxylic acid bis-N,N'-[(2-benzoyloxyethyl)amide]

Analogously to Example 5a)
Colorless needles, melting point 139-140°C
Empirical formula: $C_{23}H_{23}N_3O_8$ (461)
MS: m/e = 462 ($M^+ + H^+$).

b) 0.31 ml of 30 perc nt strength H_2O_2 is added dropwise to a solution of 0.46 g of pyridine-2,4-dicarboxylic acid N,N'-bis-[(2-benzoyloxy)ethyl]amide (Example 6a)) in 5 ml of 96 percent strength formic acid, and the mixture is heated at 80°C for 4 hours, while stirring. After addition of a further 0.2 ml of H_2O_2, the mixture is stirred at this temperature for a further 2 hours and then evaporated in vacuo, and the residue is purified by chromatography over silica gel using ethyl acetate as the eluent. 0.37 g of pyridine-1-oxide-2,4-dicarboxylic acid N,N-bis-[(2-benzoyloxyethyl)amide] is obtained as colorless crystals, melting point 159-160°C (methanol).
MS: m/e = 478 ($M^+ + H^+$).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A substituted pyridine N-oxide of the formula I



(I)

in which

R^1 and R^3 or R^4 are $-C(O)-X-R^6$, in which
X is O or $-N(R^7)-$ and
R^6 and R^7 are identical or different, and

A are a branched or unbranched, aliphatic or cycloaliphatic (C_1-C_{12})-alkyl radical or (C_1-C_{12})-alkenyl radical or a (C_1-C_{12})-alkynyl radical,

which is unsubstituted or mono- or polysubstituted, preferably mono- or disubstituted, by halogen, in particular fluorine, chlorine or bromine, hydroxyl, cyano, carboxyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoyl-

amino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, N,N-di-(C_1-C_8)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, are substituted by 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, hydroxy, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, trifluoromethyl, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl and N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR', or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical or heteroaryl radical which carries 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, nitro, cyano, carboxyl, hydroxyl, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl,

benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy-carbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyl-oxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcar-bonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkyl-carbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoyl-amino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmer-capto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenyl-sulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido and arylsulfonamido, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyc-lic in nature and/or, as is also the case for alkyl, can be substituted by 1,2,3,4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, hydroxyl, (C_1-C_8)-hydroxyalkyl and (C_1-C_8)-alkoxy, or by

an unsubstituted or substituted (C_6-C_{12})-aryloxy radical, (C_7-C_{11})-aralkyloxy radical or heteroaryloxy radical, which carries 1, 2, 3, 4 or 5 identical or different substitu nts from the s ries comprising hydroxyl, halo-gen, cyano, nitro, trifluoromethyl, (C_1-C_8)-alkyl, (C_1-C_8)-hydroxyalkyl, (C_1-C_8)-alkoxy, $[CH_2-]_xC_fH_{(2f+1-g)}F_g$,

$-OCF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl and N-di-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl, is optionally substituted by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR', or by

a radical of the general formula II

$$-O-R^8 \qquad (II)$$

in which

R^8 is an amino acid bonded via its acyl radical, a derivative of this amino acid or an alcohol-protective group,

B are an unsubstituted or substituted (C_6-C_{12})-aryl radical or (C_7-C_{11})-aralkyl radical or a heteroaryl radical, which is mono- or polysubstituted, preferably mono- or disubstituted, by

hydroxyl, halogen, cyano, carboxyl, amino, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkoxycarbonyl, (C_1-C_8)-alkylcarbonyl, (C_1-C_8)-alkylcarbonyloxy, (C_1-C_8)-alkylamino, di-(C_1-C_8)-alkylamino, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, aminoalkyl, N-(C_1-C_8)-alkylamino-(C_1-C_{12})-alkyl or N,N-di-(C_1-C_8)-

alkylamino-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, cinnamoyl, cinnamoyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_8)-alkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{11})-aralkanoylamino, (C_1-C_8)-alkanoyl-(C_1-C_8)-alkylamino, (C_3-C_8)-cycloalkanoyl-(C_1-C_8)-alkylamino, (C_6-C_{12})-aroyl-(C_1-C_8)-alkylamino, (C_7-C_{11})-aralkanoyl-(C_1-C_8)-alkylamino, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, nitro, trifluoromethyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, (C_1-C_8)-alkyl-sulfonamido or arylsulfonamido,

C in the case where X = -N(R'), are an unsubstituted or substituted (C_1-C_{12})-alkoxy radical, (C_3-C_8)-cycloalkoxy radical or (C_6-C_{12})-aryloxy radical or a (C_7-C_{11})-aralkyloxy radical, which is mono- or polysubstituted, preferably mono- or disubstituted, by

halogen, trifluoromethyl, (C_1-C_6)-alkoxy, hydroxyl, (C_1-C_6)-hydroxyalkyl, NR'R" or cyano,

in which, in each case,

R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkylcarbonyl, (C_7-C_{11})-aralkylcarbonyl or (C_6-C_{12})-arylcarbonyl

or form a saturated heterocyclic ring, preferably a 5- or 6-membered ring, with the nitrogen,

and

R^2, R^5 and R^4 or R^3, if R^4 or R^3 has not already been defined above, are identical or different and

D are hydrogen, at least one radical R^2, R^5 and R^4 or R^3 being other than hydrogen, halogen, in particular fluorine, chlorine or bromine, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_3-C_8)-cycloalkyl, phenylmercapto, phenylsulfonyl, phenylsulfinyl, (C_1-C_{12})-alkoxycarbanoyl, (C_1-C_{12})-alkylcarbanoyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino-(C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-alkynylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_8)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_8)-dialkylamino, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, NR'R", (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, sulfamoyl,

N-(C_1-C_6)-alkylsulfamoyl, N,N-di-(C_1-C_6)-alkylsulfamoyl, (C_1-C_8)-alkylsulfonamido or arylsulfonamido, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or are substituted, as is also the case for alkyl, with 1, 2, 3, 4 or 5 identical or different substituents from the series comprising halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, -O-[CH_2-]$_x$$C_fH_{(2f+1-g)}F_g$, -$OCF_2Cl$, -O-$CF_2$-CHFCl, trifluoromethyl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, NR'-R", phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl and N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or

E are an alkyl, alkenyl or alkynyl radical having up to 9 carbon atoms, which is optionally substituted by

1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, [CH_2-]$_x$$C_fH_{(2f+1-g)}F_g$, -$OCF_2CHFCl$, ($C_1$-$C_6$)-alkylmercapto, ($C_1$-$C_6$)-alkylsulfinyl, ($C_1$-$C_6$)-alkylsulfonyl, ($C_1$-$C_6$)-alkylcarbonyl, ($C_1$-$C_6$)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_6)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-

(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{11})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cyclo-alkanoylamino, (C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or by an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_tH_{(2t+1-s)}F_s$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_{10})-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cyclo-alkanoylamino, (C_1-C_{12})-hydroxyalkanoylamino, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino, in particular by up to 3 of the abovementioned identical or different substituents, and a CH_2 group of the alkyl chain is optionally replaced by O, S, SO, SO_2 or NR',

or

F denote a substituted or unsubstituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore

carries in the aryl part 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino, morpholino, thiomorpholino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular up to 3 of the abovementioned identical or different substituents, and in which a CH_2 group of the aryl chain is optionally replaced by O, S, SO, SO_2 or NR', or

G are a substituent of the formulae $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen, alkyl, alkenyl or alkynyl, in each case having up to 9 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which

carri s in the aryl part 1, 2, 3, 4 or 5 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, carboxyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2CHFCl$, (C_1-C_6)-alkyl-

m rcapto, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino, morpholino, thiomorpholino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, in particular up to 3 of the abovementioned identical or different substituents, and in which a CH_2 group of the aryl chain is optionally replaced by O, S, SO, SO_2 or NR',

and

n = 0 or 1,

f = 1 to 8, preferably 1 to 5,

g = 0.1 to (2f + 1) and

x is 0, 1, 2 or 3, preferably 0 or 1,

or any derivative which contains a corresponding protective group in its amino or hydroxyl groups, or a physiologically active salt.

2. A compound as claimed in claim 1, in which
R^1 and R^3 or R^4 are $-C(O)-X-R^6$, in which
X is $-N(R^7)-$.

3. A compound as claimed in claim 1 or 2, in which
R^6 is hydrog n or methyl and
R^7 has th meaning given in claim 1, or
R^6 and R^7 ar hydrogen and/or methyl, if at l ast one group R^1, R^3 or R^4 is a radical $-C(O)-N(R^7)-R^6$,

in which R^6 and/or R^7 have the meaning given in claim 1.

4. A compound as claimed in claim 1 or 2, in which R^6 and R^7

A are a branched or unbranched (C_1-C_{12})-alkyl radical, which is unsubstituted or mono- or polysubstituted by

halogen, in particular fluorine, chlorine, bromine, hydroxyl, cyano, carboxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarboxyl, (C_1-C_8)-alkoxycarbonyloxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkyloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_7-C_{11})-arylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, carbamoyloxy, N-(C_1-C_8)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_7-C_{11})-aralkylcarbamoyloxy or N-(C_6-C_{12})-arylcarbamoyloxy, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature, and/or, as is also the case for alkyl, are substituted by 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, hydroxyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_3)-alkoxycarbonyl, carbamoyl, (C_1-C_8)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from the series comprising halogen, nitro, cyano, carboxyl, hydroxyl, trifluoromethyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, $NR'R''$, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_1-C_3)-alkylcarbonyloxy, aminoalkyl and N-(C_1-C_4)-alkylamino-(C_1-C_8)-alkyl, in which R' and R" ar identical or different and are hydrogen, (C_6-C_{12})-aryl or (C_1-C_4)-alkyl, or by

an unsubstituted or substituted (C_6-C_{10})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical, which carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_3)-alkyl, (C_1-C_3)-hydroxyalkyl, (C_1-C_3)-alkoxy, (C_1-C_3)-alkylmercapto, (C_1-C_3)-alkylsulfinyl, (C_1-C_3)-alkylsulfonyl, (C_1-C_3)-alkylcarbonyl, (C_1-C_3)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_3)-alkylcarbonyloxy and NR'R", in which R' and R" are identical or different and are hydrogen, (C_6-C_{10})-aryl or (C_1-C_4)-alkyl, or by

a radical of the formula II

$$-O-R^8 \qquad (II)$$

in which

R^8 is an amino acid bonded via its acyl radical, or is a derivative thereof,

B denote a (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical, preferably phenyl, benzyl or phenethyl, which are unsubstituted or monosubstituted by halogen, cyano, carboxyl, hydroxyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, (C_1-C_8)-alkylcarbonyl, (C_1-C_4)-alkylcarbonyloxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-hydroxyalkyl, amino, (C_1-C_5)-alkylamino, di-(C_1-C_5)-alkylamino, (C_1-C_5)-alkanoylamino, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyloxy or N,N-di-(C_1-C_4)-alkylcarbamoyloxy or

C are an unsubstituted (C_1-C_6)-alkoxy radical, (C_3-C_8)-cycloalkoxy radical, (C_6-C_{12})-aryloxy radical or (C_7-C_{11})-aralkyloxy radical.

5. A compound as claimed in any of claims 1 to 4, in which R^2, R^5 and R^4 or R^3, if R^4 and R^3 ar not already

defined in Claims 1 to 4 and are not to be hydrogen, are

D halogen, in particular fluorine, chlorine or bromine, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-G)}F_G$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_3-C_8)-cycloalkyl, (C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy. amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino, piperidino or their heterocyclic derivatives morpholino and thiomorpholino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{11})-aralkylcarbonylamino, (C_1-C_6)-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{11})-aralkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_3-C_8)-alkenylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-amino, (C_1-C_{12})-alkoxy-N-(C_1-C_6)-alkylamino, (C_1-C_{12})-alkoxy-N,N-(C_1-C_6)-dialkylamino, carbamoyloxy, N-(C_1-C_6)-alkylcarbamoyloxy, N,N-di-(C_1-C_8)-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, $NR'R''$, (C_1-C_8)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_8)-alkylsulfonyl, (C_1-C_8)-alkylcarbonyl or (C_3-C_8)-cycloalkylcarbonyl, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, are substituted by 1, 2 or 3 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-G)}F_G$, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, $NR'R''$, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl,

or

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substitut d by 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2-CHFCl$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_6)-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_6)-alkanoylamino, (C_1-C_6)-alkoxy-(C_1-C_6)-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino, or by an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy, $[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, carboxyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_6)-alkylamino, N-(C_7-C_{11})-aralkylamino, N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, (C_1-C_6)-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_1-C_6)-hydroxyalkanoylamino, (C_1-C_6)-alkoxy-(C_1-C_6)-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino,

or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in

which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, cyano, nitro, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino,

or

G a substituent of the formula $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen, alkyl or alkenyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which carries 1, 2 or 3 identical or different substituents from the series comprising halogen, hydroxyl, cyano, nitro, carboxyl, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, (C_1-C_{10})-alkanoylamino, (C_6-C_{12})-arylcarbonylamino and (C_7-C_{11})-aralkylcarbonylamino.

6. A compound as claim d in any of claims 1 to 5, in which

R^2, R^5 and R^4 or R^3, if R^4 and R^3 are not already defined above and are not to be hydrogen, are

D halogen, in particular fluorine, chlorine or bromine, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino or N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, in which the aryl and aralkyl radicals present in the above substituents can also be heterocyclic in nature and/or, as is also the case for alkyl, can be substituted by 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, hydroxyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$ and NR'-R, or

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substituted by 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino and di-N,N-(C_1-C_6)-alkylamino, or by

an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, phenyl, benzyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino, di-N,N-(C_1-C_6)-alkylamino or N,N-(C_3-C_8)-alkanediylamino, such as, for example, pyrrolidino or piperidino, or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, in which the aryl and heteroaryl radical mentioned is, in particular, phenyl, naphthyl, thienyl, furyl, pyrrolyl or pyridine, and which furthermore carries 1, 2 or 3 identical or different substituents from the series comprising hydroxyl, halogen, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, ($C_1$-$C_8$)-alkylcarbonyl, ($C_1$-$C_8$)-alkoxycarbonyl, amino, N-(C_1-C_{10})-alkylamino and di-N,N-(C_1-C_{10})-alkylamino, or

G a substituent of the formula $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen or alkyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which contains 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, amino, N-($C_1$-$C_{10}$)-alkylamino and di-N,N-(C_1-C_{10})-alkylamino.

7. A compound as claimed in any of claims 1 to 6, in which

R^2, R^5 and R^4 or R^3, if R^4 and R^3 are not already defined in any of claims 1 to 4 and are not to be hydrogen, are

D halogen, in particular fluorine, chlorine or bromine, trifluoromethyl, (C_1-C_{12})-alkyl, $-O-[CH_2-]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_8)-alkylcarbonyl, (C_3-C_8)-cycloalkyl, amino, N-(C_1-C_{10})-alkylamino, di-N,N-(C_1-C_{10})-alkylamino, N-(C_6-C_{12})-arylamino, N-(C_6-C_{12})-aryl-N-(C_1-C_8)-alkylamino, N-(C_7-C_{11})-aralkylamino or N-(C_7-C_{11})-aralkyl-N-(C_1-C_{10})-alkylamino, or:

E an alkyl or alkenyl radical having up to 5 carbon atoms, which is optionally substituted by 1 or 2 identi-

cal or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, phenoxy, benzyloxy, amino, N-(C_1-C_6)-alkylamino and di-N,N-(C_1-C_6)-alkylamino, or by an unsubstituted or substituted (C_6-C_{12})-aryl radical, (C_7-C_{11})-aralkyl radical or heteroaryl radical, which carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylcarbonyl and (C_1-C_6)-alkoxycarbonyl, or

F an unsubstituted or substituted (C_6-C_{12})-aryl radical or (C_7-C_{11})-aralkyl radical, in which the aryl radical mentioned is, in particular, phenyl or naphthyl and which furthermore carries 1 or 2 identical or different substituents from the series comprising hydroxyl, halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, carboxyl, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkylcarbonyl and (C_1-C_6)-alkoxycarbonyl, or

G a substituent of the formula $-OR^9$ or $-N(R^9)_2$, in which

R^9 is hydrogen or alkyl having in each case up to 6 carbon atoms, a (C_6-C_{12})-aryl radical or a heteroaryl radical, which contains 1 or 2 identical or different substituents from the series comprising halogen, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, amino, N-(C_1-C_{10})-alkylamino and di-N,N-(C_1-C_{10})-alkylamino.

8. A process for the preparation of the compound as claimed in any of claims 1 to 7, which comprises reacting a compound of the formula V or VI with an oxidizing agent in an organic solvent at a temperature of between -30 and +40°C to give a compound of the formula I.

9. A compound as claimed in any of claims 1 to 7 for inhibiting proline hydroxylase and lysine hydroxylase.

10. A compound as claimed in any of claims 1 to 7 for use as a fibrosuppressant and immunosuppressant.

11. A medicament comprising a compound of the formula I and a tolerated pharmaceutical excipient.

12. The use of a compound of the formula I for influencing the metabolism of collagen and collagen-like substances and the biosynthesis of Cl_q.

13. The use of a compound of the formula I for the treatment of disturbances in the metabolism of collagen and collagen-like substances and the biosynthesis of Cl_q.

14. A process for the preparation of a medicament for influencing the metabolism of collagen and collagen-like substances and the biosynthesis of Cl_q, wherein the medicament comprises a compound of the formula I.